REMARKS

Claims 3, 4 and 20 are pending and under examination in the above-identified application.

Regarding 35 U.S.C. § 103

Applicants respectfully traverse the rejection of claims 1 (now new claim 20), 3 and 4 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Nagao et al., Tetrahedron Letters, 41, 2419-2424, (2000), in view Mackay EA et al., Eur J. Biochem. Mar 1; 244(2):414-25, (1997).

Briefly, base claim 3 is directed to a method of selecting an agent that prevents cleavage of a substrate comprising APP, said method comprising the steps of contacting a candidate agent with a β-secretase species selected from the group consisting of cathepsin B and cathepsin L, wherein the contacting occurs in the presence of a substrate comprising APP and under conditions that allow for cleavage of the APP by said β-secretase species; and selecting the agent that prevents the cleavage of the APP by the β-secretase species.

The Examiner contends that it would have been obvious to modify the assay taught by Nagao et al. and substitute the cathepsin B peptide substrate, Z-L-Phe-L-Arg-MCA, with APP, because Mackay et al. teach that APP is a substrate for cathepsin B. Applicants respectfully argue that, not only would there have been no motivation to combine with a reasonable expectation of success, the cited references in fact teach away from the claimed invention.

A prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), cert. denied, 469 U.S. 851 (1984). A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant." *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994); *see KSR,* 127 S. Ct. at 1739–40 (explaining that when the prior art teaches away from a combination, that combination is more likely to be nonobvious).

Mackay et al. at p.415, left hand column, first paragraph:

> The specificity of proteases for their native substrates may not only be determined by the amino acid sequence but also by the conformation of the protein/peptide. It is therefore desireable to use native substrate rather than a short peptide whenever possible. In addition, the use of the native substrate allows one whether or not to establish not only whether a certain cleavage can occur but also whether such a cleavage is preferred.

Applicants maintain that there would have been no motivation to combine the two cited prior art references, which clearly show that the substrate used in the assays described by Nagao et al., which is a dipeptide capped at both ends, is distinct from the cleavage sites recognized by cathepsin B in the APP protein. Figure 6, panel C, shows the cleavage sites recognized by cathepsin B and not one of them consists of the amino acids F – Phenylalanine (Phe/F) and R - Arginine (Arg/R) that make up the dipeptide of Nagao et al. There is no indication in Nagao et al. that the assay would work if the short dipeptide were to be replaced with a considerably longer substrate that does not even contain the Phe-Arg cleavage site known in the art to be recognized by cathepsin B.

As described by Mackay et al. (see above-quoted excerpt), the specificity of cathepsin B and other proteases is determined by a number of factors and the native substrate is the preferred indicator of cleavage studies. Given the dependence of protease activity on amino acid and conformation of the substrate, a skilled person would have appreciated that cleavage as well as inhibition of cleavage must be studied with a substrate comprising APP. The skilled person would have further been discouraged from exchanging the dipeptides of Nagao et al. with a substrate comprising APP in view of the fact that the Mackay reference teaches both amino acid and conformation of the substrate are important for β-secretase specificity. Furthemore, the Mackay et al. reference shows that the β-secretase activity of cathepsin B implicates substrate cleavage sites different and distinct from those of the dipeptide substrate used by Nagao et al. Based on these express teachings, the skilled person would not expect the assay of Nagao et al. to work with the APP substrate of Mackay et al., which lacks the Phe-Arg recognition site. Any substrate that would be used to replace the Nagao et al. dipeptide would be selected based on the presence of a Phe-Arg recognition site that APP lacks. Figure 6, panel C, shows one of cathepsin cleavage sites consist of the amino acids F – Phenylalanine (Phe/F) and R - Arginine (Arg/R)

that make up the dipeptide of Nagao et al. In this regard, a reference may teach away from a use when that use would render the result inoperable. *McGinley v. Franklin Sports, Inc.*, 262 F.3d 1339, 1354 (Fed. Cir. 2001).

Applicants respectfully request removal of the rejection of claims 1 (now new claim 20), 3 and 4 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Nagao et al., Tetrahedron Letters, 41, 2419-2424, (2000), in view Mackay EA et al., Eur J. Biochem. Mar 1; 244(2):414-25, (1997).

CONCLUSION

In light of the Remarks herein, Applicants submit that the claims are in condition for allowance and respectfully request a notice to this effect. Should the Examiner have any questions, he is invited to call the undersigned attorney.

To the extent necessary, a petition for an extension of time under 37 C.F.R. 1.136 is hereby made. Please charge any shortage in fees due in connection with the filing of this paper, including extension of time fees, to Deposit Account 502624 and please credit any excess fees to such deposit account.

Respectfully submitted,

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